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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/810,976	03/26/2004	Won-Bin Young	P05768US01	9933

22885 7590 12/22/2005

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EXAMINER	
RIGGINS, PATRICK S	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 12/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/810,976	YOUNG ET AL.	
	Examiner	Art Unit	
	Patrick S. Riggins	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,15,18-25,29-73 and 76-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,15,18-25,29-73 and 76-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/4/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Receipt is acknowledged of an amendment filed 10/3/05. Claims 1, 9, 10, 23, 24, 35, 36, 38, 40, 50, and 57 were amended. Claims 12-14, 16, 17, 26-28, 74, and 75 were canceled. New claims 76-80 were added. Presently claims 1-11, 15,18-25, 29-73, and 76-80 are pending and under examination.

Specification

2. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. These are particularly noted on pages 18 and 31. Applicant has amended to replace "www." with "world wide web at ". This does not correct the deficiency noted in the Office Action mailed 6/29/05. The portion of the web address that renders it browser executable code is the http:// reference. Thus is would be remedial to amend to --www.ncbi.nlm.nih.gov/--.

Claim Rejections - 35 USC § 112-1

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection. This is a new rejection necessitated by the amendment to the claims.

5. Claim 1 has been amended to recite: "subjecting said cDNA fragment to a DNA polymerase and nucleotides to generate a blunt-ended fragment". The specification lack literal support for this limitation in the claim. The amendment points to paragraph 114 of the published specification for support of this limitation. The support in paragraph 114 is for filling in with "Klenow enzyme". Thus this portion of the specification does not provide support for the genus of "a DNA polymerase" it only provides support for the species of "Klenow enzyme".

6. Claim 79 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new rejection necessitated by applicant's amendment to the claims.

7. Claims 79 recites, at the bottom of page 30, cutting to "generate sequence tags of at least 8 nucleotides". As claimed this encompasses cleaving to generate any tag of any length greater than 8 nucleotides, including tags of 30, 40, 60, 100, 1000 nucleotides. The specification does not provide a structural basis for any enzyme that could cleave DNA and leave a tag of any greater than 20 nucleotides. Indeed the maximum unknown tag of any Type IIs enzyme disclosed is 20 nucleotides in length. Further the prior art teaches that the maximum length of any as yet identified type IIs restriction enzyme is 20 nucleotides. "They [Type IIs enzymes] cleave at a defined distance, up to 20 base pairs, to one side of their recognition sequence" (New England

BioLabs 1998/99 Catalog, page 12, end of column 2). It is thus clear that the specification and the prior art teach only of type IIs enzymes that can cleave 20 bases away from the recognition sequence, and thus the specification does not establish possession of any type IIs recognition site or type IIs enzyme that could leave a sequence tag of greater than 20 base pairs. It would thus be remedial to replace "at least 8 nucleotides" with --8 to 20 nucleotides--.

Claim Rejections - 35 USC § 112-2

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 10, 11, 15, 18-25, 29-47, and 76-80 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. This is an existing rejection, however it is newly applied to newly entered claims 76-80.

10. The omitted steps are: For claims 36, 76, 77, and 79 a step is missing prior to the step of "self-ligating the cDNA fragment." As a type IIs restriction enzyme cuts outside of the non-palindromic recognition site and generally cuts leaving an overhang, the nature of the overhang is unknown. As the construct is specifically designed to cut within the unidentified, adjacent exons, it is highly unlikely that the two overhangs would have compatible cohesive ends. To successfully achieve self-ligation, the unidentified cohesive ends must first be filled in to create blunt ends. Only after this step would self-ligation even be possible.

11. Regarding claims 10, 24, 38, 40, 78, and 80, these claims lack essential elements pertaining to the linkers to be ligated to the type IIs cleaved fragments. For the practice of the

invention it is essential that the linkers comprise an appropriate number of randomized overhang nucleotides to allow for ligation of the liners to the unidentified overhangs produced by the type IIs enzymes. Again, as the type IIs restriction enzyme cleaves the cDNA in a region with unknown sequence and type IIs enzymes tend to leave an overhang, that in this case, the sequence of which would be unknown, it is necessary to account for the lack of a blunt end. In order to successfully ligate linkers onto the unknown cDNA tag end, the randomized overhang is a requirement.

Response to Arguments

12. Applicant's arguments filed 10/3/05 have been fully considered but they are not persuasive. Claim 1 was amended to correct the deficiency that blunting of the unknown overhang is necessary, however newly entered claims 76, 77, and 79 failed to incorporate this essential step.

13. Applicant's argument pertaining to the lack of a necessity for a restriction enzyme site in the linkers on page 37, first full paragraph of the amendment, is persuasive. The argument regarding the need to include randomized ends in the linkers is not found persuasive. This argument can be found in the second full paragraph of page 37 of the amendment. Applicant states that the skilled artisan would know of cloning using blunt-ended fragments such as after PCR. While this is indeed true, it in no way addresses the needs for ligating a linker onto an unknown cohesive end of a cleaved cDNA. It is noted however that while blunting of the unknown overhang prior to ligation of the linkers would indeed be a possible way to attach the linkers without needing a randomized overhang, the only apparent method for ligating linkers to

the unknown overhangs was through the use of randomized bases in the linkers (see Example 3). Further, in order to first blunt the overhang prior to ligation of linkers, this would require unrecited steps that would be required to practice the invention in this manner. To introduce these new steps would be considered to be impermissible new matter, as there is no discussion of this sort of treatment in the specification.

14. Claims 1-11, 15, 18-25, 29-47, 79, and 80 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

15. Claims 1, 10, 24, 36, 38, 40, 79, and 80 all recite, when referring to the two restriction sites at both the 5' end and the 3' end, that "at least one of the RER sites is recognized by a Type IIs restriction enzyme." This is vague and indefinite because it implies that the other RER site could also be a Type IIs enzyme. This would neither be desirable not effective. The second RER sites are present to allow for the cleavage of the PCR product to generate "a linear DNA fragment containing upstream and downstream exon tags fused in an inverted conformation". This then allows either the insertion of the fragment into a sequencing vector, or for concatamerization prior to insertion into a sequencing vector. For either of these to successfully take place the overhangs produced must be known and have an appropriate cohesiveness. As a Type IIs enzyme leaves overhangs that would differ for almost any two different Type IIs recognition sites they would not be an effective choice for the second RER site present at each end of the marker. To delete the term "one of" in each of these cases would be remedial. It is noted that neither of claims 76 or 77 are subject to this particular rejection.

Response to Arguments

16. Applicant's arguments filed 10/3/05 have been fully considered but they are not persuasive. Applicant states at the top of page 39 of the amendment, that the position of the Office is that the second restriction sites at the exon boundaries cannot be type IIs restriction enzyme sites. This is not the case. No assertion has been made the second restriction sites could not be type IIs merely that the skilled artisan would have no desire to use a type IIs enzyme for the purpose states for the second restriction sites at the exon boundaries. In the paragraph spanning pages 39 and 40, Applicant argues that the ends of a second enzyme would be known and could be appropriately dealt with. The skilled artisan would be able to use direct ligation, linkers, or blunt ending.

17. First, direct ligation has an extremely low likelihood of success because although the artisan would indeed know the sequence of the overhang if the cleavage were to occur in a known sequence, there is no sequence restriction where the overhangs would be consistent between the 5' and 3' ends. Thus, unless the marker exon construct was specifically designed in that manner, a possibility that has not apparently been contemplated in the specification, direct ligation would have a low likelihood of success.

18. Further, while linkers or blunting of the ends is also a possibility, either of these possibilities would require additional necessary steps that are not present in the claims, and which further have not apparently been contemplated in the original specification, and to add these necessary steps would constitute impermissible new matter.

19. Claims 10, 11, 15, and 18-25, 29-35, 38-41, and 44-47 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

20. Claim 10 recites the limitation "subjecting the cDNA to a Type IIs restriction enzyme that recognizes one Type IIs RER site located at the 5' end of the marker exon and cleaving the cDNA upstream of the 5' end of the marker exon". This is vague and indefinite because it is unclear what is fully intended by this limitation as only one Type IIs restriction site has been identified previously at the 5' end that cuts upstream of the 5' end of the exon. By reciting one type IIs site, this implies a second type IIs site that cuts in the region upstream of the exon has been previously recited in the claims. As this is not the case, reciting one type IIs site essentially constitutes a lack of antecedent basis for the term. Claims 24, 38, and 40 have this same issue.

Response to Arguments

21. Applicant's arguments filed 10/3/05 have been fully considered but they are not persuasive. Applicant has emended to replace "one of the" with "one". As states above in paragraph 18, this implies that a second site has been recited in the claims prior to the cleaving step. The recited "one Type IIs" site is required to cut upstream of the marker exon. It would be highly undesirable for a second type IIs site to direct cutting upstream of the exon. Indeed in Applicant's argument on page 41, first paragraph, Applicant has stated that only one type IIs site directs the type IIs enzyme to cut upstream of the exon, if a second type IIs site were used, it would not be directed to promote cutting in the unknown region. Thus even by applicant's own argument, there is only one type IIs site at the 5' end of the marker exon that leas to cutting

upstream of the marker exon. Thus the metes and bounds of this limitation in the claim are unclear. To replace "one Type IIs RER site" with --the Type IIs RER site-- or --said Type IIs RER site-- would be remedial.

22. Claims 36, 37, 42, and 43 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

23. Claim 36 is vague and indefinite because it recites "RNA tags" in the second to last line on page 15 of the amended claims. It is unclear what is intended by this limitation as the tags in question are not composed of RNA, but instead consist of cDNA. Thus the skilled artisan would be unable to determine the metes and bounds of this claim limitation.

Response to Arguments

24. Applicant's arguments filed 10/3/05 have been fully considered but they are not persuasive. Applicant has amended the first appearance of "RNA tags" to "nucleotide sequence tags". Only the first appearance of "RNA tags" has been amended. The second appearance still recites "RNA tags" without proper antecedent basis. Thus, the rejection is maintained.

25. Claims 76-80 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This is a new rejection necessitated by applicant's amendment to the claims.

26. Claims 76-80 each recite the limitations "isolating said RNA" and "reverse transcribing the isolated mRNA". There is insufficient antecedent basis for either of these limitations in the claims.

27. The only previous mention of RNA in the claims is in the preamble where "a RNA transcriptional profile" is sought. Thus the preamble does not provide antecedent basis for RNA, but rather of a "transcriptional profile". It would be remedial to replace "said RNA" with –mRNA--. This would correct both antecedent basis deficiencies in these claims.

28. Claims 76, 77, and 79 each recite "the first Type IIs restriction enzymes" in the second section starting with "subjecting". The prior steps in the claims only recite a single enzyme or enzymes uses in concert. To recite "the first" implies a second has been used. As this is clearly not the case, this limitation essentially lacks antecedent basis. It is noted that claims 78 and 80 are not subject to this particular rejection.

29. The indicated allowability of claims 48, 49, and 51-73 is withdrawn in view of the newly discovered reference(s) US 2003/0143578 and US. Patent No 6,897,020. Rejections based on the newly cited reference(s) follow.

Claim Rejections - 35 USC § 102

30. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

31. Provisional application 60/458,152 provides support for SAVI, but does not provide support for the present incarnation of 5' SAVI or 3' SAVI. As such all claims regarding 5' and 3" SAVI are treated as having the priority date of the instant application, i.e. 3/26/04.

32. Claims 24, 25, 29-35, 40, 41, 46-54, 62-66, 68-73, and 80 are rejected under 35 U.S.C. 102(a) and under 35 U.S.C. 102(e) as being anticipated by Pruitt (US 2003/0143578, of record).

33. The claims are drawn to polynucleotide constructs comprising splice acceptors, splice donors, type IIs restriction sites, other restriction sites, marker exons, and potentially poly adenylation signals and selection markers downstream of the exons. The constructs can be comprised in a vector. The marker exon can encode a fluorescent protein that can be green fluorescent protein. The type IIs restriction sites can be BsmFI or MmeI sites. The other restriction sites can be BamHI sites. The claims are further drawn to methods of 3' SAVI wherein a polynucleotide as described above is introduced into cells, mRNA is isolated, cDNA is synthesized, the cDNA is cut with a type IIs restriction enzyme that cuts downstream of the marker exon. A linker is then ligated to the cleaved cDNA and this cleaved product is then amplified. The nucleic acid sequence of the cleaved tags is identified and the sequence information is considered against a database. In the method, the construct can be contained in a vector which can be a retroviral or adeno-associated vector. The exon can encode a fluorescent marker, including GFP which is measure by flow cytometry.

34. Pruitt discloses vectors for identifying transcribed genes, wherein a splice acceptor is followed by a type IIs restriction site which is position to allow for cutting upstream of the spliced exon. Next is another restriction site, followed by the nucleotide sequence of a fluorescent reporter, which is followed by a polyadenylation signal. Next is a neomycin resistance cassette, followed by a restriction site, another type IIs restriction site positions to cut downstream of the spliced exon, and a splice donor (see Figure 1A). The construct can be included in a vector which can be retroviruses or adenoassociated viruses (see paragraph 0031 and the end of paragraph 0043). The fluorescent proteins can be EGFP or GFP (see paragraph 0029). The enzymes that recognize the type IIs restriction sites can be a number of enzymes that leave up to 20 base pairs outside the recognition signal including BsmFI and MmeI (see paragraph 0040). The enzyme that recognizes the non-type IIs sites can be BamHI (see Figure 1A).

35. The vector was transfected into cells by electroporation and the EGFP was detected and measured by flow cytometry (see Example 2). The mRNA is isolated, cDNA is made, and the Type IIs enzyme to cut the 3' end of the exon is used. An adaptor is ligated to the cleaved cDNA and this is then amplified by PCR. Following amplification, the products are cut with the non-type IIs restriction enzyme, concatamerized, and cloned into a vector for sequencing (see paragraphs 0061, 0062, and 0083). The sequences of the concatamers are then compared to a sequence matrix/database (see paragraph 0066 and 0067). Thus Pruitt anticipates each limitation of the rejected claims.

Claim Rejections - 35 USC § 103

36. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

37. Claims 55-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pruitt.

38. The claims are drawn to a polynucleotide construct as above except the type IIs restriction sites are positioned internally to the other restriction sites. S this is simply a variation of the vector discloses in Pruitt, it would have been an obvious design choice to construct the construct in this manner. On would have been motivated to make the construct in the3 manner claimed because one may wish to shuttle the exon intact into different vectors. By placing the other restriction site outside of the type IIs sites, this can be performed while maintaining the orientation of all parts with relative ease. Thus, the vector of claims 55-61 is merely an obvious variant of the vector in claims 48-54.

39. Claims 48, 54, 55, 61, 62, and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pruitt in view of the 1998/99 NEB catalog.

40. The claims are drawn to the constructs as described above wherein the on-type IIs restriction sites can be NcoI or NheI.

41. Pruitt discloses the limitations of the constructs as described above, but does not disclose specifically using NcoI or NheI as the non-type IIs restriction sites.

42. The NEB catalog discloses the well-known fact that different restriction enzymes are largely functionally equivalent differing only in the recognition sequence they will cleave. As such the skilled artisan would have been motivated to use other restriction enzymes such as NcoI or NheI because the choice of different restriction enzyme sites is merely a matter of preference. It would have been obvious to one of ordinary skill in the art to use different restriction enzymes, such as NcoI or NheI as taught by the NEB catalog in the vectors of Pruitt if the sequences present in the constructs were more conducive to these other enzymes. As different restriction enzymes are essentially functionally equivalent, to make these changes would have a reasonable expectation of success.

43. Claims 10, 11, 15, 18-23, 38, 39, 44, 45, and 78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pruitt in view of U.S. Patent No. 6,897,020 (hereinafter Link, of record)

44. The claims are drawn to a method of 5'SAVI, which is similar to 3' SAVI except that after first strand synthesis the first strand is extended with a terminal transferase such that after second strand synthesis and cleavage with the 5' type IIs restriction enzyme. A linker is then added and the 5' end is amplified using a primer complementary to the linker and another complementary to the marker exon. After amplification, the product is cleaved with the other restriction enzyme at the 5' end of the marker exon and this fragment, or a concatamer of this fragment is then ligated into a vector for sequencing and sequence analysis. All of the same limitations pertaining to the nature of the vector apply in this case as well.

45. Pruitt discloses the method for 3' identification as described above and discloses that the for 3' identification as described above and discloses that the 5' end of the exon can also be examined for sequence tags (see Figure 1A and paragraphs 0040, 0043, and 0061).

46. Pruitt does not disclose the steps in the method where a terminal transferase is used prior to cleavage and amplification.

47. Link discloses 5' SAVI where terminal transferase is used to extend the 5' end of the exon after cleavage (see Figure 17; column 7, line 37-column 8, line 6; and column 31). One would have been motivated to use terminal transferase as taught by Link in the 5' analysis method of Pruitt because this provides an alternative to linker ligation which requires randomized nucleotides to hybridize with the unknown cohesive ends produced by the type IIs enzyme. This allows for a straightforward standardization of the protocol. Therefore it would have been obvious to one of ordinary skill in the art to use a terminal transferase as taught by Link in the sequence tag identification method of Pruitt with a reasonable expectation of success.

48. Claims 10, 11, 15, 18-25, 29-35, 38-41, 44-73, 78, and 80 are rejected under 35 U.S.C. 103(a) as being obvious over Link in view of Pruitt.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter

disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

49. Link discloses and claims a method of SAVI as instantly claimed (See Figure 17). Link discloses vectors for SAVI where a marker exon is flanked by splice acceptor with a type IIs restriction enzyme site positioned to cut upstream of the marker exon, a marker sequence that can encode a fluorescent protein including Green Fluorescent Protein (see claims 18 and 19). The marker sequence is optionally followed by either a polyadenylation sequence or a splice donor, with a type IIs restriction site juxtaposed such that the type IIs restriction enzyme will cut downstream of the marker exon. A selection marker can be placed downstream of the marker exon (see Figure 2, particularly 2D). The marker construct can be included in a vector including a retroviral vector, and adenoviral vector, and a lentiviral vector (see Figure 2 and claims 21 and 22). The construct above is transfected into cells (see column 12, lines 46-53, and column 34, lines 12-33), cells are identified by flow cytometry (claim 12), and mRNA is isolated. After cDNA synthesis, the cDNA is cut with the type IIs restriction enzyme. After adapter addition which can be either through ligation or terminal transferase tailing, the cleaved fragment is ligated into concatamers, sequenced and the expression profile of the cell is identified (see Figure 17; column 7, line 45-column 8, line 6; column 31; and claims 1, 4, and 7-9).

50. Link does not disclose constructs that further comprise additional restriction sites adjacent to the type IIs sites, and consequently also does not disclose the steps of cleaving with restriction enzymes that recognize these sites in order to facilitate the concatamerization or direct subcloning of the isolated sequence tags.

51. Pruitt discloses constructs for use in sequence tag identification. The constructs of Pruitt have a splice acceptor followed by a type IIs restriction site, followed by another restriction site. Next is a fluorescent marker that can be used to track transfected cells by flow cytometry. A second marker is next, followed by a restriction site, a second type II restriction site, and a splice donor (see Figure 1A and paragraphs 0022, 0029, 0038, and 0040). After cleavage with the type IIs enzyme, linker ligation and amplification, the other restriction enzyme that recognizes and cleaves the other restriction site is used to facilitate concatamerization and subcloning into a vector for sequencing (see paragraphs 0059, 0061-0063, 0067, 0082, and 0083).

52. At the time of the invention, one would have been motivated to modify the construct of Link by adding a second restriction site adjacent to the type IIs restriction site as taught by Pruitt in the SAVI method of Link because a cohesive end ligation is a more efficient than a blunt end ligation and thus would facilitate analysis of the cloned sequence tags. Therefore it would have been obvious to one of ordinary skill in the art to combine the teachings of Link with those of Pruitt in order to better facilitate the identification and analysis of the cloned sequence tags.

Double Patenting

53. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is

appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

54. Claims 10, 11, 15, 18-25, 29-35, 38-41, 78, and 80 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 4, 7, 9, 12, and 18-22 of U.S. Patent No. 6,897,020 in view of Pruitt, as follows: instant claims 10, 24, 38, 40, 78, and 80 over patent claims 4 and 7, instant claims 11, 25, 29, 39, and 41 over patent claim 9, instant claims 15 and 29 over patent claim20, instant claims18, and 30 over patent claim 21, instant claims 19, 20, 31, and 32 over patent claim 22, instant claims 21, 22, 33, and 34 over patent claim 18, and instant claims 23 and 35 over patent claim 12.

55. The patent claims are drawn to SAVI which can be either 5' SAVI or 3' SAVI. The methods in the patent claims are essentially identical to those in the instant claims. The only substantive difference is a lack of a second restriction site at either the 5' or 3' end of the marker exon aside from the type IIs restriction site. The patent claims refer to the use of a construct with a type IIs restriction site adjacent to a splice acceptor. The patent claims do not teach the inclusion of a second restriction site near the type IIs site to allow for future processing.

56. Pruitt discloses (see Figure 1A and paragraphs 0040, 0043, 0059, 0061-0063, 0067, 0082, and 0083) a method of SAVI for both the 5' end of a marker exon and the 3' end of a marker

exon. The methods of Pruitt use constructs with both type IIs restriction sites for acquiring sequence tags, and other restriction sites for later cloning in the method.

57. One would have been motivated to combine the methods of Pruitt with the claimed method of the '020 patent because the inclusion of additional restriction sites adjacent to the type IIs restriction sites allows for ease of later cloning and subsequent identification of the sequence tags. Therefore the instant claims are an obvious variant of the patent claims when viewed in light of Pruitt.

58. Claims 10, 11, 15, 18-25, 29-35, 38-41, 78, and 80 are directed to an invention not patentably distinct from claims 4, 7, 9, 12, and 18-22 of commonly assigned 6,897,020. Specifically, the claims are not considered to be patentably distinct for the reasons set forth in paragraphs 54-57 above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned 6,897,020, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly

assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Conclusion

59. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. U.S. Patent No. 6,136,566 discloses constructs comprising a selectable marker flanked by both a splice acceptor and a splice donor. These constructs are used to mutate and tag genes, where the tagged regions can be sequenced. The '566 patent does not disclose using type IIs restriction sites in order to obtain short sequence tags.

60. All new grounds of rejection presented in the instant Office Action were either prompted by the submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 10/4/05, or were necessitated by applicant's amendment to the claims. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b) and MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick S. Riggins whose telephone number is (571) 272-6102. The examiner can normally be reached on M-F 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patrick Riggins, Ph.D.
Examiner
Art Unit 1633